HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XHANCE® safely and effectively. See full prescribing information for XHANCE®.

XHANCE® (fluticasone propionate) nasal spray, for intranasal use
Initial U.S. Approval: 1994

----------INDICATIONS AND USAGE----------

XHANCE is a corticosteroid indicated for the treatment of nasal polyps in patients 18 years of age or older. (1)

----------DOSAGE AND ADMINISTRATION----------

- For intranasal use only. XHANCE is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing into the mouthpiece of the device. (2.2)
- Recommended adult dosage: One spray per nostril twice daily (total daily dose of 372 mcg). Two sprays per nostril twice daily may also be effective in some patients (total daily dose of 744 mcg). (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Nasal spray: 93 mcg of fluticasone propionate in each 106-mg spray. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to any ingredient in XHANCE. (4)

----------WARNINGS AND PRECAUTIONS----------

- Local Nasal Effects: epistaxis, erosion, ulceration, septal perforation, *Candida albicans* infection, and impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcerations, nasal surgery, or nasal trauma. (5.1)
- Close monitoring for glaucoma and cataracts is warranted. (5.2)
- Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, contact dermatitis, rash, hypotension, and bronchospasm) have been reported after administration of fluticasone propionate. Discontinue XHANCE if such reactions occur. (5.3)
- Immunosuppression: potential increased susceptibility to or worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.4)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue XHANCE slowly. (5.5)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 3%) are epistaxis, nasal septal ulceration, nasopharyngitis, nasal mucosal erythema, nasal mucosal ulcerations, nasal congestion, acute sinusitis, nasal septal erythema, headache, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact OptiNose US, Inc. at 1-833-678-6673 and safety@optinose.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole): Use not recommended. May increase risk of systemic corticosteroid effects. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Monitor patients for signs of increased drug exposure. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XHANCE® nasal spray is indicated for the treatment of nasal polyps in patients 18 years of age or older.

2 DOSAGE AND ADMINISTRATION

2.1 Nasal Polyps

Adults (18 years and older): The recommended dosage of XHANCE nasal spray is 1 spray (93 mcg of fluticasone propionate per spray) in each nostril twice daily (total daily dose, 372 mcg). A dose of 2 sprays (93 mcg of fluticasone propionate per spray) in each nostril twice daily may also be effective in some patients (total daily dose, 744 mcg). The maximum total daily dosage should not exceed 2 sprays in each nostril twice daily (total daily dose, 744 mcg).

Patients should use XHANCE at regular intervals since its effectiveness depends on regular use. Individual patients will experience a variable time to onset and different degrees of symptom relief.

The safety and efficacy of XHANCE when administered in excess of recommended doses have not been established.

2.2 Administration Information

Administer XHANCE by the intranasal route only, avoiding spraying directly on the nasal septum. Shake XHANCE before each use. Before initial use, prime XHANCE by first gently shaking and then pressing the bottle 7 times or until a fine mist appears. Direct the spray into the air, away from the face. When XHANCE has not been used for ≥ 7 days, prime the pump again by shaking and releasing 2 sprays into the air, away from the face.

XHANCE is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing (exhaling) into the mouthpiece of the device. To administer XHANCE, insert the tapered tip of the cone-shaped nosepiece deep into one nostril and form a tight seal between the nosepiece and the nostril. Next, place the flexible mouthpiece into the mouth, bending it as necessary to maintain a tight seal. Blow into the mouthpiece, and while continuing to blow, push the bottle up to actuate the spray pump. Continuing to blow through the mouth, but not inhaling or exhaling through the nose, at the time of actuation is important to achieve intended drug deposition. Repeat the process in the other nostril for a full dose.

3 DOSAGE FORMS AND STRENGTHS

Nasal spray: Each 106-mg spray delivers 93 mcg of fluticasone propionate. One unit provides 120 metered sprays.

4 CONTRAINDICATIONS

XHANCE is contraindicated in patients with hypersensitivity to any of the ingredients [*see Warnings and Precautions (5.3) and Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Local Nasal Effects

<u>Epistaxis, Nasal Erosions and Ulcerations</u>

In placebo-controlled clinical trials of 16 weeks duration, epistaxis, nasal erosions, and nasal ulcerations were reported more frequently in patients treated with XHANCE than those who received placebo [*see Adverse Reactions (6.1)*].

Nasal Septal Perforation

Nasal septal perforations have been reported in patients following the intranasal application of XHANCE. In placebo-controlled clinical trials of 16 weeks duration, nasal septal perforations were reported in 1 (0.3%) patient treated with XHANCE compared with none treated with placebo. The patient had a prior history of nasal/sinus surgery. Three (0.3%) patients treated with XHANCE in uncontrolled, open-label trials of 3 to 12 months duration developed nasal septal perforations.

As with any long term topical treatment of the nasal cavity, patients using XHANCE over several months or longer should be examined periodically for possible changes in the nasal mucosa. If a septal perforation is noted, discontinue XHANCE. Avoid spraying XHANCE directly on the septum.

Candida Infection

In clinical trials with XHANCE, localized infections with *Candida albicans* have been observed. Eight (0.9%) patients in uncontrolled, open-label trials of 3 to 12 months duration developed *Candida albicans* infections (nasal, pharyngeal, esophageal or intestinal). If such an infection develops, it may require treatment with appropriate local therapy and discontinuation of XHANCE. Patients using XHANCE should be examined periodically for evidence of *Candida* infection in the nasal and oropharyngeal mucosa.

Impaired Wound Healing

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcerations, nasal surgery, or nasal trauma should avoid using XHANCE until healing has occurred.

5.2 Glaucoma and Cataracts

Nasal and inhaled corticosteroids, including fluticasone propionate, may result in the development of glaucoma and/or cataracts. In placebo-controlled clinical trials of 16 weeks duration, cataracts were reported in 4 (1.2%) patients treated with XHANCE, compared with 3 (1.9%) patients treated with placebo. Among these patients, 2 patients treated with XHANCE reported subcapsular cataracts compared with none treated with placebo. Eleven patients (1.2%) in uncontrolled, open-label trials of 3 to 12 months duration developed new or worsening cataracts, of which none were subcapsular. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure (IOP), glaucoma, and/or cataracts.

5.3 Hypersensitivity Reactions Including Anaphylaxis

XHANCE is contraindicated in patients with known hypersensitivity to fluticasone propionate or any of the ingredients of XHANCE. Discontinue XHANCE if such reactions (e.g., anaphylaxis, angioedema, urticaria, contact dermatitis, rash, hypotension, and bronchospasm) occur [*see Contraindications (4) and Adverse Reactions (6.1)*].

5.4 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals and may experience a worsening of existing infections. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible adults using corticosteroids. In such adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection

is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex [*see Adverse Reactions (6.1)*].

5.5 Hypothalamic-Pituitary-Adrenal Axis Effects

Hypercorticism and adrenal suppression may occur when intranasal corticosteroids, such as XHANCE, are used at higher than recommended dosages or in susceptible individuals at recommended dosages. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, recommended dosages of XHANCE should not be exceeded to avoid hypothalamic-pituitary-adrenal (HPA) dysfunction. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of pulmonary treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing XHANCE.

Patients treated with XHANCE should be observed carefully for any evidence of systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis). If such effects occur, the dosage of XHANCE should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of nasal symptoms should be considered. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. In addition, some patients may experience symptoms of corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression). After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress such as trauma, surgery, infection (particularly gastroenteritis), or other conditions associated with severe electrolyte loss. In patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, rapid decreases in systemic corticosteroid dosages may cause a severe exacerbation of their symptoms *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.2)]*.

5.6 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole) with XHANCE is not recommended because increased systemic corticosteroid adverse effects may occur [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term oral inhalation of products containing corticosteroids into the lungs. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated with established standards of care.

A 2-year trial in 160 subjects (females aged 18 to 40 years, males aged 18 to 50 years) with asthma receiving chlorofluorocarbon (CFC)-propelled fluticasone propionate inhalation aerosol 88 or 440 mcg twice daily demonstrated no statistically significant changes in BMD at any time point (24, 52, 76, and 104 weeks of double-blind treatment) as assessed by dual-energy x-ray absorptiometry at lumbar regions L1 through L4.

5.8 Effect on Growth

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. The safety and efficacy of XHANCE has not been established in pediatric patients [*see Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Local nasal effects: epistaxis, erosion, ulceration, septal perforation, *Candida albicans* infection, and impaired wound healing [*see Warnings and Precautions (5.1)*]
- Cataracts and glaucoma [*see Warnings and Precautions (5.2)*]
- Hypersensitivity reactions including anaphylaxis [*see Contraindications (4) and Warnings and Precautions (5.3)*]
- Immunosuppression [*see Warnings and Precautions (5.4)*]
- HPA axis effects, including growth reduction [*see Warnings and Precautions (5.5* and *5.8)*]
- Reduction in bone mineral density [*see Warnings and Precautions (5.7)*]
- Effect on Growth [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below are based on two placebo-controlled clinical trials evaluating doses of a fluticasone propionate nasal spray with an exhalation delivery system from 93 mcg twice daily to 372 mcg twice daily. Both trials were 16-weeks in duration with an additional 8-week open-label extension. The trials included a total of 643 adult subjects with bilateral nasal polyps and associated moderate or severe nasal congestion of which 161 received 93 mcg twice daily, 160 received 186 mcg twice daily, 161 received 372 mcg twice daily and 161 received placebo. The overall pooled safety data included 296 (46.0%) Female, 347 (54.0%) Male, 584 (90.8%) White, 39 (6.1%) Black, 9 (1.4%) Asian, and 11 (1.7%) subjects classified as Other. Of these patients, 45 (7%) were 65 years of age or older.

Table 1 displays adverse reactions with an incidence of ≥ 3% in the XHANCE 186 mcg and 372 mcg twice daily subjects, and more common than placebo.

Table 1. Summary of Adverse Reactions with XHANCE Reported in ≥ 3% of Subjects with Nasal Polyps and More Common Than Placebo in Placebo-Controlled Studies			
		XHANCE	
Adverse Reaction	**Placebo (N = 161) n (%)**	**186 mcg bid (N = 160) n (%)**	**372 mcg bid (N = 161) n (%)**
Epistaxis[1]	4 (2.5)	19 (11.9)	16 (9.9)
Nasopharyngitis	8 (5.0)	3 (1.9)	12 (7.5)
Nasal septal ulceration[2]	3 (1.9)	11 (6.9)	12 (7.5)
Nasal congestion	6 (3.7)	7 (4.4)	9 (5.6)
Acute sinusitis	6 (3.7)	7 (4.4)	8 (5.0)
Headache	5 (3.1)	8 (5.0)	6 (3.7)
Pharyngitis	2 (1.2)	2 (1.3)	5 (3.1)
Nasal mucosal ulceration[2]	2 (1.3)	6 (3.8)	4 (2.5)
Nasal mucosal erythema	6 (3.7)	9 (5.6)	8 (5.0)
Nasal septal erythema	3 (1.9)	6 (3.8)	7 (4.3)

bid = twice daily.
[1]Includes spontaneous adverse reaction reports
[2]Include ulcerations and erosions

Other adverse reactions with XHANCE observed with an incidence < 3% but ≥ 1% and more common than placebo included: nasal dryness, sinusitis, oropharyngeal pain, toothache, intraocular pressure increase, dizziness, abdominal discomfort, and weight increase.

5.0% of subjects treated with XHANCE 186 mcg twice daily and 1.2% of subjects treated with 372 mcg twice daily discontinued from the clinical trials prior to the open-label extension because of adverse reactions compared to 4.3% of subjects treated with placebo.

There were no clinically relevant differences in the incidence of adverse reactions based on gender. Clinical trials did not include sufficient numbers of non-Caucasian patients or patients aged 65 years and older to determine whether they respond differently from Caucasian or younger patients, respectively.

The adverse reactions observed during uncontrolled, open-label trials of 3 to 12 months duration in subjects with chronic sinusitis with and without nasal polyps receiving XHANCE 372 mcg twice daily were similar to the adverse reactions reported in clinical trials in patients with nasal polyps.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate is a substrate of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin, conivaptan, lopinavir, voriconazole) with XHANCE is not recommended because increased systemic corticosteroid adverse effects may occur.

Ritonavir

A drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure,

resulting in significantly reduced serum cortisol concentrations [*see Clinical Pharmacology (12.3)*]. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate products with ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.

Ketoconazole

Coadministration of orally inhaled fluticasone propionate (1000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC), but had no effect on urinary excretion of cortisol.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published literature on the use of inhaled or intranasal fluticasone propionate in pregnant women have not reported a clear association with adverse developmental outcomes. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight, and/or skeletal variations in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate less than the maximum recommended human daily inhaled dose (MRHDID) on a mcg/m^2 basis. However, fluticasone propionate administered via inhalation to rats decreased fetal body weight, but did not induce teratogenicity at a maternal toxic dose less than the MRHDID on a mcg/m^2 basis (*see Data*). Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryofetal development studies with pregnant rats and mice dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate was teratogenic in both species. Omphalocele, decreased body weight, and skeletal variations were observed in rat fetuses, in the presence of maternal toxicity, at a dose approximately equivalent to the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 100 mcg/kg/day). The rat no observed adverse effect level (NOAEL) was observed at approximately 0.4 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 30 mcg/kg/day). Cleft palate and fetal skeletal variations were observed in mouse fetuses at a dose approximately 0.3 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 15 mcg/kg/day).

In an embryofetal development study with pregnant rats dosed by the inhalation route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.34 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal inhalation dose of 5.5 mcg/kg/day).

In an embryofetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reductions of fetal body weights, in the presence of maternal toxicity, at doses approximately 0.02 times the MRHDID and higher (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate for 1 fetus at a dose approximately 0.1 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.002 times the MRHDID (on a mcg/m^2 basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits.

In a pre- and post-natal development study in pregnant rats dosed from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to 0.7 times the MRHDID (on a mcg/m^2 basis with maternal subcutaneous doses up to 50 mcg/kg/day).

8.2 Lactation

Risk Summary

There are no available data on the presence of fluticasone propionate in human milk, the effects on the breastfed child, or the effects on milk production. Fluticasone propionate is present in rat milk *(see Data)*. Other corticosteroids have been detected in human milk. However, fluticasone propionate concentrations in plasma after orally inhaled therapeutic doses are low, and therefore, concentrations in human breast milk are likely to be correspondingly low [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XHANCE and any potential adverse effects on the breastfed child from XHANCE or from the underlying maternal condition.

Data

Subcutaneous administration of tritiated fluticasone propionate at a dose in lactating rats approximately 0.1 times the MRHDID for adults (on a mcg/m^2 basis) resulted in measurable levels in milk.

8.4 Pediatric Use

The safety and efficacy of XHANCE in pediatric patients have not been established.

Effects on Growth

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. This effect was observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies.

Controlled clinical trials have shown that corticosteroids orally inhaled into the lungs may cause a reduction in growth in pediatric patients. In these trials, the mean reduction in growth velocity was approximately 1 cm/year

(range: 0.3 to 1.8 cm/year) and appeared to depend upon dose and duration of exposure. The effects on growth velocity of treatment with corticosteroids orally inhaled into the lungs for over 1 year, including the impact on final adult height, are unknown. The growth of children and adolescents receiving corticosteroids should be monitored routinely (e.g., via stadiometry) [*see Warnings and Precautions (5.8)*].

8.5 Geriatric Use

Clinical trials of XHANCE did not include sufficient numbers of subjects aged 65 years and older to determine whether they responded differently than younger subjects. Other reported clinical experience with fluticasone administered intranasal or orally inhaled has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Formal pharmacokinetic trials using XHANCE have not been conducted in subjects with hepatic impairment. Since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

8.7 Renal Impairment

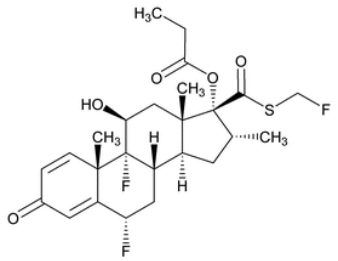
Formal pharmacokinetic trials using XHANCE have not been conducted in subjects with renal impairment.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism [*see Warnings and Precautions (5.5)*]. An intranasal dose of 2 mg (2.7 to 5.4 times the recommended daily dose) of fluticasone propionate twice daily for 7 days was administered to healthy human volunteers. Adverse events reported with fluticasone propionate were similar to placebo, and no clinically significant abnormalities in laboratory safety tests were observed. Single oral doses up to 16 mg have been studied in human volunteers with no acute toxic effects reported. Oral inhalation by healthy volunteers of a single dose of 1.76 or 3.52 mg of fluticasone propionate was well tolerated. Fluticasone propionate given by pulmonary inhalation administration at dosages of 1.32 mg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups.

11 DESCRIPTION

The active component of XHANCE is fluticasone propionate, a corticosteroid, having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.57, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and dichloromethane, and slightly soluble in 96% ethanol.

XHANCE (fluticasone propionate) nasal spray, 93 mcg, for intranasal administration, contains an exhalation delivery system that delivers an aqueous suspension of microfine fluticasone propionate having a particle size distribution in the range of 0 to 5 microns for topical intranasal administration by means of a metering, atomizing spray pump and exhaled breath. XHANCE also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, and purified water, and has a pH between 5 and 7.

Before initial use, prime XHANCE by gently shaking and then pressing the amber glass bottle 7 times or until a fine mist appears. Once primed, XHANCE contains 120 metered sprays. When XHANCE has not been used for ≥ 7 days, prime again by releasing 2 sprays into the air, away from the face [*see Dosage and Administration (2.2) and patient Instructions for Use*].

After priming, each spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece. The system also has a flexible mouthpiece. Within the device is a non-removable amber glass bottle with a metering spray pump, an applicator, and a valve that prevents release of breath until the bottle is pressed. A removable orange cap covers both the nosepiece and mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fluticasone propionate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone propionate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is 18 times that of dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results. The clinical significance of these findings is unknown.

The precise mechanism through which fluticasone propionate affects nasal polyps and associated inflammatory symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. The anti-inflammatory action of corticosteroids contributes to their efficacy. In 7 trials in adults, fluticasone propionate nasal spray decreased nasal mucosal eosinophils in 66% of patients (35% for placebo) and basophils in 39% of patients (28% for placebo). In addition, studies suggest that carbon dioxide, which is present in the exhaled breath delivered into the nose through the device, may influence inflammatory mediator activity and neuropeptide activity, possibly through mechanisms of action that also include removal of nitric oxide, change in pH, or positive pressure. The direct relationship of these findings to long-term symptom relief is not known.

12.2 Pharmacodynamics

<u>HPA Axis Effect</u>

The potential systemic effects of XHANCE on the HPA axis have not been evaluated.

Serum cortisol concentrations, urinary excretion of cortisol, and urine 6-β- hydroxycortisol excretion collected over 24 hours in 24 healthy subjects following 8 oral inhalations of fluticasone propionate 44, 110, and 220 mcg decreased with increasing dose. However, in patients with asthma treated with 2 oral inhalations of fluticasone propionate 44, 110, and 220 mcg twice daily for at least 4 weeks, differences in serum cortisol $AUC_{0\text{-}12h}$ (n =

65) and 24-hour urinary excretion of cortisol (n = 47) compared with placebo were not related to dose and generally not significant.

The potential systemic effects of orally inhaled fluticasone propionate on the HPA axis were also studied in subjects with asthma [*see Warnings and Precautions (5.5) and Adverse Reactions (6)*]. Fluticasone propionate given by oral inhalation aerosol at dosages of 440 or 880 mcg twice daily was compared with placebo in oral corticosteroid-dependent subjects with asthma (range of mean dose of prednisone at baseline: 13 to 14 mg/day) in a 16-week trial. Consistent with maintenance treatment with oral corticosteroids, abnormal plasma cortisol responses to short cosyntropin stimulation (peak plasma cortisol less than 18 mcg/dL) were present at baseline in the majority of subjects participating in this trial (69% of subjects later randomized to placebo and 72% to 78% of subjects later randomized to fluticasone propionate HFA). At week 16, 8 subjects (73%) on placebo compared with 14 (54%) and 13 (68%) subjects receiving fluticasone propionate HFA (440 and 880 mcg twice daily, respectively) had poststimulation cortisol levels of less than 18 mcg/dL.

Cardiac Electrophysiology

A study specifically designed to evaluate the effect of XHANCE on the QT interval has not been conducted.

12.3 Pharmacokinetics

The activity of XHANCE is due to the parent drug, fluticasone propionate. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data were obtained via other routes of administration.

Absorption

The mean (SD) peak exposure (C_{max}) and total exposure ($AUC_{0-\infty}$) following administration of a dose of 186 mcg of XHANCE during exhalation were 17.2 ± 7.40 pg/mL and 111.7 ± 49.75 pg•h/mL, respectively, and were 25.3 ± 10.34 pg/mL and 171.7 ± 85.55 pg•h/mL, respectively, following a dose of 372 mcg of XHANCE in healthy subjects. The C_{max} and $AUC_{0-\infty}$ following a dose of 372 mcg of XHANCE in patients with mild to moderate asthma were 28.7±18.72 pg/mL and 222.6±84.60 pg•h/mL, respectively.

Distribution

Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 99%. Fluticasone propionate is weakly and reversibly bound to erythrocytes and is not significantly bound to human transcortin.

Local exposure within the nasal cavity with XHANCE will differ when used without exhalation through the device.

Elimination

Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. The total blood clearance of fluticasone propionate is high (average: 1093 mL/min), with renal clearance accounting for less than 0.02% of the total.

Metabolism: The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the CYP3A4 pathway. This metabolite had less affinity (approximately 1/2000) than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations

XHANCE was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Pediatrics: XHANCE was not studied in pediatric patients, and no pediatric-specific pharmacokinetic data have been obtained with the product.

Hepatic and Renal Impairment: Formal pharmacokinetic studies using XHANCE have not been conducted in patients with hepatic or renal impairment. However, since fluticasone propionate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of fluticasone propionate in plasma. Therefore, patients with hepatic disease should be closely monitored.

Race: No significant difference in clearance (CL/F) of fluticasone propionate in Caucasian, African-American, Asian, or Hispanic populations has been observed.

Drug Interactions

Inhibitors of Cytochrome P450 3A4

Ritonavir: Fluticasone propionate is a substrate of CYP3A4. Coadministration of fluticasone propionate and the strong CYP3A4 inhibitor, ritonavir, is not recommended based upon a multiple-dose, crossover drug interaction trial in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (< 10 pg/mL) in most subjects, and when concentrations were detectable, peak levels (C_{max}) averaged 11.9 pg/mL (range: 10.8 to 14.1 pg/mL) and $AUC_{0-\tau}$ averaged 8.43 pg•h/mL (range: 4.2 to 18.8 pg•h/mL). Fluticasone propionate C_{max} and $AUC_{0-\tau}$ increased to 318 pg/mL (range: 110 to 648 pg/mL) and 3102.6 pg•h/mL (range: 1207.1 to 5662.0 pg•h/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in serum cortisol AUC.

Ketoconazole: Coadministration of fluticasone propionate orally inhaled into the lungs (1000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

Following orally-inhaled fluticasone propionate alone, AUC_{2-last} averaged 1559 pg•h/mL (range: 555 to 2906 pg•h/mL) and $AUC_{2-\infty}$ averaged 2269 pg•h/mL (range: 836 to 3707 pg•h/mL). Fluticasone propionate AUC_{2-last} and $AUC_{2-\infty}$ increased to 2781 pg•h/mL (range: 2489 to 8486 pg•h/mL) and 4317 pg•h/mL (range: 3256 to 9408 pg•h/mL), respectively, after coadministration of ketoconazole with orally-inhaled fluticasone propionate. This increase in plasma fluticasone propionate concentration resulted in a decrease (45%) in serum cortisol AUC.

Erythromycin: In a multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1000 mcg/kg (approximately 7 times the MRHDID for adults on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (approximately equivalent to the MRHDID for adults on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the in vivo mouse micronucleus test.

Fertility and reproductive performance were unaffected in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 0.7 times the MRHDID for adults on a mcg/m^2 basis).

14 CLINICAL STUDIES

14.1 Treatment of Nasal Polyps in Adults 18 Years of Age and Older

The efficacy of XHANCE was evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled, dose-ranging trials in adults 18 years and older with nasal polyps and associated moderate to severe nasal congestion (NCT 01622569, NCT 01624662). The two trials included a total of 646 subjects [348 (53.9%) males and 298 (46.1%) females] with a mean age of 45.5 years. Subjects were randomized 1:1:1:1 to receive 93 mcg, 186 mcg, or 372 mcg twice daily or placebo for a period of 16 weeks. At baseline 35.7%, 79.0%, and 18.3% had polyps graded as mild, moderate, or severe, respectively. In addition, 90.6% of patients reported previous use of a topical steroid nasal spray for the treatment of nasal polyps and 53.6% reported previous sinus surgery or polypectomy.

The co-primary efficacy endpoints were 1) change from baseline to Week 4 in nasal congestion / obstruction averaged over the preceding 7 days of treatment and 2) change from baseline to Week 16 in bilateral polyp grade. Nasal congestion was rated by the patient on a 0 to 3 categorical severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) at the time immediately prior to the next dose (instantaneous). Polyp grade was determined by the clinician using nasal endoscopy. Polyps on each side of the nose were graded on a categorical scale (0 = No polyps; 1 = Mild – polyps not reaching below the inferior border of the middle turbinate; 2 = Moderate – polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate; 3 = Severe – large polyps reaching below the lower inferior border of the inferior turbinate).

Efficacy was demonstrated for both XHANCE 186-mcg twice daily and XHANCE 372-mcg twice daily (Table 2).

Table 2: Effect of XHANCE nasal spray in two randomized, placebo-controlled trials in patients with nasal polyps.

	XHANCE 186-mcg bid	XHANCE 372-mcg bid	Placebo	Diff. (95% CI) XHANCE 186-mcg bid vs placebo	Diff. (95% CI) XHANCE 372-mcg bid vs placebo
Trial 1 (N)	80	79	82		
Baseline nasal congestion LS mean change from baseline in nasal congestion at week 4	2.24 -0.54	2.29 -0.62	2.31 -0.24	-0.30 (-0.48, -0.11)	-0.38 (-0.57, -0.19)
Baseline total bilateral polyp grade	3.9	3.7	3.8		

LS mean change from baseline in total bilateral polyp grade at week 16	-1.03	-1.06	-0.45	-0.59 (-0.93, -0.24)	-0.62 (-0.96, -0.27)
Trial 2 (N)	80	82	79		
Baseline nasal congestion LS mean change from baseline in nasal congestion at week 4	2.20 -0.68	2.25 -0.62	2.29 -0.24	-0.45 (-0.64, -0.25)	-0.38 (-0.58, -0.18)
Baseline total bilateral polyp grade LS mean change from baseline in total bilateral polyp grade at week 16	3.9 -1.22	3.9 -1.41	3.8 -0.61	-0.60 (-0.89, -0.31)	-0.80 (-1.08, -0.51)
bid= twice daily					

There were no clinically relevant differences in effectiveness of XHANCE across subgroups of patients defined by gender, age, or race.

Onset of action, evaluated by determining the starting period that the treatment effect of XHANCE on daily instantaneous AM congestion score started to achieve statistical significance in comparison to placebo and roughly maintained thereafter, was generally observed within 2 weeks for both XHANCE doses.

16 HOW SUPPLIED/STORAGE AND HANDLING

XHANCE (fluticasone propionate) nasal spray is supplied as a non-removable amber glass bottle fitted with a metered-dose manual spray pump unit inside the white XHANCE device with a nasal applicator, valve mechanism, asymmetrical cone-shaped nosepiece, flexible mouthpiece, and orange cap in a box of 1 (NDC 71143-375-01) with FDA-approved Patient Labeling [for proper use, see patient *Instructions for Use*].

Each bottle contains a net fill content of 16 mL, and after priming will provide 120 metered sprays. Each metered spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece. The correct amount of medication in each metered spray cannot be assured after 120 metered sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of metered sprays has been used.

Store at room temperature (between 15°C and 25°C; 59°F and 77°F), excursions permitted from 15°C to 30°C (59°F to 86°F). Avoid exposure to extreme heat, cold or light. Shake XHANCE before each use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Local Nasal Effects

Inform patients that treatment with XHANCE may lead to adverse reactions, which include epistaxis, nasal erosions, and nasal ulceration. *Candida* infection may also occur with treatment with XHANCE. In addition, XHANCE has been associated with nasal septal perforation and impaired wound healing. Patients who have experienced recent nasal ulcerations, nasal surgery, or nasal trauma should not use XHANCE until healing has occurred [*see Warnings and Precautions (5.1)*].

Glaucoma and Cataracts

Inform patients that glaucoma and cataracts are associated with long-term use of nasal and orally inhaled corticosteroids, including fluticasone propionate, and may increase the risk of some eye problems. Consider regular eye exams. Advise patients to notify their healthcare providers if a change in vision is noted while using XHANCE [*see Warnings and Precautions (5.2)*].

Hypersensitivity Reactions, Including Anaphylaxis

Inform patients that hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, contact dermatitis, rash, bronchospasm, and hypotension, may occur after administration of fluticasone. If such reactions occur during use with XHANCE, patients should discontinue use of the product [*see Warnings and Precautions (5.3)*].

Immunosuppression

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles, and if they are exposed to consult their healthcare provider without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex [*see Warnings and Precautions (5.4)*].

Hypercorticism and Adrenal Suppression

Advise patients that XHANCE may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to XHANCE [*see Warnings and Precautions (5.5)*].

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased bone mineral density that the use of corticosteroids may pose an additional risk [*see Warnings and Precautions (5.7)*].

Reduced Growth Velocity

The safety and efficacy of XHANCE use in pediatric patients has not been established. Inform patients that corticosteroids administered by oral inhalation into the lungs or intranasally may cause a reduction in growth velocity when administered to pediatric patients [*see Warnings and Precautions (5.8)*].

Use Twice Daily for Best Effect

Inform patients that they should use XHANCE on a regular basis as directed. XHANCE, like other corticosteroids, does not have an immediate effect on nasal polyps or symptoms. Individual patients will experience a variable time to onset and degree of symptom relief and the full benefit may not be achieved until treatment has been administered for up to 16 weeks or longer. Maximum benefit may not be reached for a period of months. Patients should not increase the prescribed dosage, but should contact their healthcare providers if symptoms do not improve or if the condition worsens.

If a patient missed a dose, the patient should be advised to take the dose as soon as they remember. The patient should not take more than the recommended dose for the day.

Keep Spray Out of Eyes and Mouth

Inform patients to avoid spraying XHANCE in their eyes and mouth.

How to Use XHANCE

It is important for patients to understand how to correctly administer XHANCE nasal spray using the exhalation delivery system. Advise the patient to carefully read the patient *Instructions for Use*. Any questions regarding use that the patient has should be directed to the physician or pharmacist.

Advise the patient to shake before each use.

The patient should note the difference in appearance of the cone-shaped, non-flexible nosepiece and the longer flexible mouthpiece.

The patient should be instructed to gently insert the tapered tip of the cone-shaped nosepiece deeply into the nose in order to gently expand the nasal passage and to create a tight seal between the nosepiece and the nostril. A seal must be maintained as the patient blows into the mouthpiece and actuates the spray pump.

To actuate the device, patients should be advised to push the bottle up while continuing to blow forcefully into the mouthpiece. Pushing the bottle up actuates the spray pump, releasing a metered dose of aerosolized medication while simultaneously allowing a “burst” of exhaled breath to pass through the device. This helps deliver the medication deep into the patient’s nose.

Patients should be advised not to try to inhale (e.g., “sniff”) when blowing (exhaling) into the mouthpiece.

Patients should be advised not to block the other nostril because the exhaled breath must pass around the back of the nasal septum and out the other side of the nose.

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PATIENT INFORMATION
XHANCE® (ex hans')
(fluticasone propionate)
nasal spray, 93 mcg

What is XHANCE?
XHANCE is a prescription medicine used to treat nasal polyps in adults.
It is not known if XHANCE is safe and effective in children.

Do not use XHANCE if you are allergic to fluticasone propionate or any of the ingredients in XHANCE. See the end of this Patient Information leaflet for a complete list of ingredients in XHANCE.

Before using XHANCE, tell your healthcare provider about all of your medical conditions, including if you:
- have or have had nasal sores, nasal surgery, or nasal injury.
- have eye problems, such as cataracts or glaucoma.
- have an immune system problem.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- have weak bones (osteoporosis).
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if XHANCE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicine in XHANCE passes into your breast milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
XHANCE and certain other medicines may interact with each other. This may cause serious side effects.
Especially tell your healthcare provider if you take antifungal or anti-HIV medicines.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use XHANCE?
Read the **Instructions for Use** leaflet for information about the right way to use XHANCE.
- Use XHANCE exactly as your healthcare provider tells you.
- **Do not** use XHANCE more often than prescribed. Ask your healthcare provider if you have any questions.
- XHANCE is for use in your nose only. **Do not spray it in your eyes or mouth.**
- XHANCE may take several days of regular use for your symptoms to get better. It may take several months for the medicine to have its greatest effect. If your symptoms do not improve or get worse, call your healthcare provider.
- You will get the best results if you keep using XHANCE regularly twice each day without missing a dose. Do not stop using XHANCE unless your healthcare provider tells you to do so.
- If you miss a dose of XHANCE, take it as soon as you remember the same day. **Do not** take more than your prescribed dose of XHANCE each day.

What are the possible side effects of XHANCE?
XHANCE may cause serious side effects, including:
- **Nasal problems**. Symptoms of nasal problems may include:
  - nose bleeds.
  - crusting in the nose.
  - sores (ulcers) in the nose.
  - hole in the cartilage of the nose (nasal septal perforation). A whistling sound when you breathe may be a symptom of nasal septum perforation.
  - thrush (candida), a fungal infection in your nose and throat. Tell your healthcare provider if you have any redness or white colored patches in your nose or mouth.
  - slow wound healing. You should not use XHANCE until your nose has healed if you have a sore in your nose, have had surgery on your nose, or if your nose has been injured.
- **Eye problems including glaucoma and cataracts**. You should have regular eye exams while you use XHANCE.
- **Serious allergic reactions**. Call your healthcare provider or get emergency medical care if you get any of the following signs of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
  - low blood pressure
- **Weakened immune system and increased chance of getting infections (immunosuppression)**. Taking medicines that weaken your immune system makes you more likely to get infections and can make certain infections worse. These infections may include tuberculosis (TB), herpes simplex infections of the eyes (ocular herpes simplex infections), and infections caused by fungi, bacteria, viruses, and parasites. Avoid contact with people who have a contagious disease such as chickenpox or measles while using XHANCE. If you come in contact with someone who

has chickenpox or measles, call your healthcare provider right away. Symptoms of an infection may include:

- fever
- pain
- aches
- chills
- feeling tired
- nausea
- vomiting

- **Reduced adrenal function (adrenal insufficiency)**. Adrenal insufficiency happens when your adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking medicine containing a steroid inhaled into the lungs or for use in the nose. Symptoms of adrenal insufficiency may include:
  - tiredness
  - weakness
  - nausea and vomiting
  - low blood pressure
- **Weak bones (osteoporosis)**.
- **Slowed growth in children**. A child's growth should be checked often.

The most common side effects of XHANCE include:

- nose bleeds
- sores (ulcers) in your nose
- pain or swelling of your nose or throat (nasopharyngitis)
- redness in your nose
- nasal congestion
- sinus infection
- headache

These are not all the side effects associated with XHANCE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XHANCE?

- Store XHANCE at room temperature between 59°F and 77°F (15°C and 25°C).
- Protect XHANCE from light.
- Throw away XHANCE after using 120 sprays after initial priming. Even though the bottle may not be completely empty, you may not get the correct dose of medicine if you continue to use it.

Keep XHANCE and all medicines out of the reach of children.

General information about the safe and effective use of XHANCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XHANCE for a condition for which it was not prescribed. Do not give your XHANCE to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about XHANCE that is written for health professionals.

What are the ingredients in XHANCE?

Active ingredient: fluticasone propionate
Inactive ingredients: microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, and purified water

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For more information, go to www.XHANCE.com or call 1-833-678-6673.

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